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Inhibition of proximal convoluted tubule transport by dopamine

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Inhibition of proximal convoluted tubule transport by dopamine.

Background. Dopamine can produce a natriuresis and diuresis independent of changes in renal hemodynamics. However, previous studies have failed to demonstrate an inhibition of transport by dopamine in intact proximal convoluted tubules.

Methods. Rabbit proximal convoluted tubules were perfused *in vitro* with an ultrafiltrate-like solution and bathed in a serum-like albumin solution.

Results. In the present study, the addition of 10^{-5} M dopamine to the lumen or bath of proximal convoluted tubules perfused *in vitro* had no effect on transport. In proximal convoluted tubules, addition of 10^{-6} M bath norepinephrine increased the rate of volume absorption from 0.65 ± 0.08 to 0.93 ± 0.08 nl/mm · min ($P < 0.01$). Addition of 10^{-5} M luminal dopamine in the presence of bath norepinephrine inhibited the rate of volume absorption to 0.72 ± 0.10 nl/mm · min ($P = 0.01$). The inhibition in the rate of volume absorption by luminal dopamine in the presence of bath norepinephrine was completely blocked by the DA_1 antagonist, SCH 23390. The DA_1 agonist luminal 10^{-5} M fenoldopam also inhibited volume absorption in the presence of bath norepinephrine, but the DA_2 agonist luminal 10^{-5} M quinpirole was without effect. Bath 10^{-5} M dopamine had no effect on volume absorption in the presence of bath norepinephrine.

Conclusion. Dopamine has no direct epithelial action on the proximal convoluted tubule. However, luminal dopamine antagonizes the stimulation in transport produced by norepinephrine. These studies suggest that luminal dopamine may play a role to modulate sodium transport in the presence of renal nerve activity.

There is compelling evidence that dopamine plays an important role in regulating extracellular fluid volume by decreasing renal sodium transport. Studies have shown a direct correlation between urinary sodium and dopamine (DA) excretion with changes in dietary sodium intake [1–4]. Acute increases in extracellular fluid volume result in an increase in urinary dopamine excretion [5–7]. Inhibition of dopamine production or action using dopamine receptor antagonists attenuate the natriuresis associated with acute volume expansion or a high salt diet [8–12]. Most of renal dopamine is produced from filtered L-dopa by L-aromatic amino acid decarboxylase [13–15], an enzyme found predominantly in the proximal tubule [8, 16, 17]. The activity of L-aromatic amino acid decarboxylase was found to be higher in rats fed a high compared to those fed a low salt diet [18]. Thus, dopamine could then act in an autocrine or paracine fashion to inhibit proximal tubule transport.

There are abundant dopamine receptors on the proximal tubule [19–27], which have been localized to both the apical and basolateral membranes [20]. Surprisingly, several studies examining the effect of dopamine have failed to demonstrate an inhibition in intact proximal convoluted tubules [28–30]. In split doplet *in vivo* proximal convoluted tubule transport studies, 10^{-4} M luminal dopamine was found to stimulate proximal tubule transport [29]. While *in vitro* microperfusion studies demonstrated a direct effect of bath dopamine to inhibit proximal straight tubule volume absorption [29, 30], comparable studies failed to demonstrate an effect on the proximal convoluted tubule [28, 30]. Studies using intact proximal tubular cells have demonstrated a stimulation of sodium uptake by dopamine [31].

In the present *in vitro* microperfusion study we reinvestigated the mechanism of action of dopamine on proximal convoluted tubule transport. We confirm that dopamine has no direct action in this segment. However, we demonstrate that luminal dopamine via DA_1 receptors has a direct epithelial action to inhibit the stimulatory action of norepinephrine on proximal tubule transport.

METHODS

Isolated segments of randomly dissected rabbit proximal convoluted tubules were perfused as previously described [32]. Briefly, kidneys from female New Zealand white rabbits were cut in coronal slices. Individual tubules were dissected in Hank's solution (4°C) containing 137 mM NaCl, 5 mM KCl, 0.8 mM $MgSO_4$, 0.33 mM Na_2HPO_4, 0.44 mM KH_2PO_4, 1 mM $MgCl_2$, 10 mM Tris-HCl, 0.25 mM $CaCl_2$, 2 mM glutamine and 2 mM L-lactate, pH 7.4. Hank's solution was gassed with 100% O_2 before use. Tubules were perfused with an ultrafiltrate-like solution containing 115 mM NaCl, 25 mM $NaHCO_3$, 2.3 mM Na_2HPO_4, 10 mM Na acetate, 1.8 mM $CaCl_2$, 1 mM $MgSO_4$, 5 mM KCl, 8.3 mM glucose, and 5 mM alanine and bathed in a similar solution

Key words: catecholamines, volume absorption, sodium transport,microperfusion, dopamine receptors, fenoldopam.

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containing 6 g/dl albumin. All bicarbonate containing solutions were bubbled with 95% O_2 and 5% CO_2 and had a pH of 7.4. The osmolality of the bath and perfusate were determined daily and adjusted to 295 mOsm/kg H_2O by the addition of either H_2O or NaCl. To maintain the pH and bath osmolality constant, bath fluid was continuously changed at the rate of at least 0.5 ml/min. All tubules were perfused at ~10 nl/min at 38°-39°C in a 1.2 ml temperature-controlled bath. The first period began after an equilibration time of at least 20 minutes. Subsequent periods were separated by an equilibration time of at least 15 minutes. Dopamine, fenoldopam and norepinephrine were weighed daily and protected from light as a solid. They were dissolved and added at the designated concentration immediately before addition to the luminal or bathing solution.

The rate of volume absorption, J_V[1] (nl/mm · min) was measured as the difference between the perfusion and collection rates normalized per millimeter of tubular length. Exhaustively dialyzed [methoxy-^{3}H] inulin was added to the perfusate at a concentration of 50 μCi/ml so that the perfusion rate could be calculated. The collection rate was measured with a 50-nl constant-volume pipette. The length, in millimeters, was measured with an eyepiece micrometer. The average tubular length was 1.4 ± 0.1 mm.

The transepithelial potential difference (PD, in millivolts) was measured using the perfusion pipette as the bridge into the tubular lumen. The perfusion and bath solutions were connected to the recording and reference calomel half-cells, respectively, via a bridge containing an ultrafiltrate-like solution in series with a 3.6 M KCl/0.9 M KNO_3 agarose bridge. This arrangement avoids direct contact of KCl/KNO_3 agarose bridges with the solution that bathed the tubule. The recording and reference calomel half-cells were connected to the high and low impedance side, respectively, of an electrometer (model 602; Keithley Instruments, Inc., Cleveland, OH, USA).

There were at least four measurements of each parameter in a given period for each tubule. The mean values for individual periods in a given tubule were used to calculate the mean value for that period. Data are expressed as a mean ± SEM. For data with three periods, analysis of variance and the Student-Newman-Keuls test were used to determine statistical significance. For experiments with two periods, a paired Student's *t*-test was used.

Quinpirole and SCH 23390 were purchased from Research Biochemicals International. Fenoldopam was a gift from Smith Kline Beecham and Neurex. All other compounds were purchased from Sigma Chemical Company.

RESULTS

Effect of dopamine on proximal convoluted tubule transport

In the first series of experiments we examined whether dopamine had a direct effect on proximal convoluted tubule transport. As is shown in Figure 1, addition of 10^{-5} M dopamine to the bathing solution had no effect on proximal convoluted tubule volume absorption (N = 5). Volume absorption was 0.70 ± 0.14 nl/mm · min in the control period and 0.81 ± 0.08 nl/mm · min after addition of 10^{-5} M bath dopamine. This concentration of dopamine has been shown to inhibit brush border membrane Na^+/H^+ antiporter activity and proximal tubule Na^+,K^+-ATPase activity [33–37]. The transepithelial potential difference was −4.8 ± 1.3 mV in the control period and −5.4 ± 1.4 mV after the addition of bath dopamine. These results confirm previous studies that bath dopamine does not affect proximal convoluted tubule transport [28, 30].

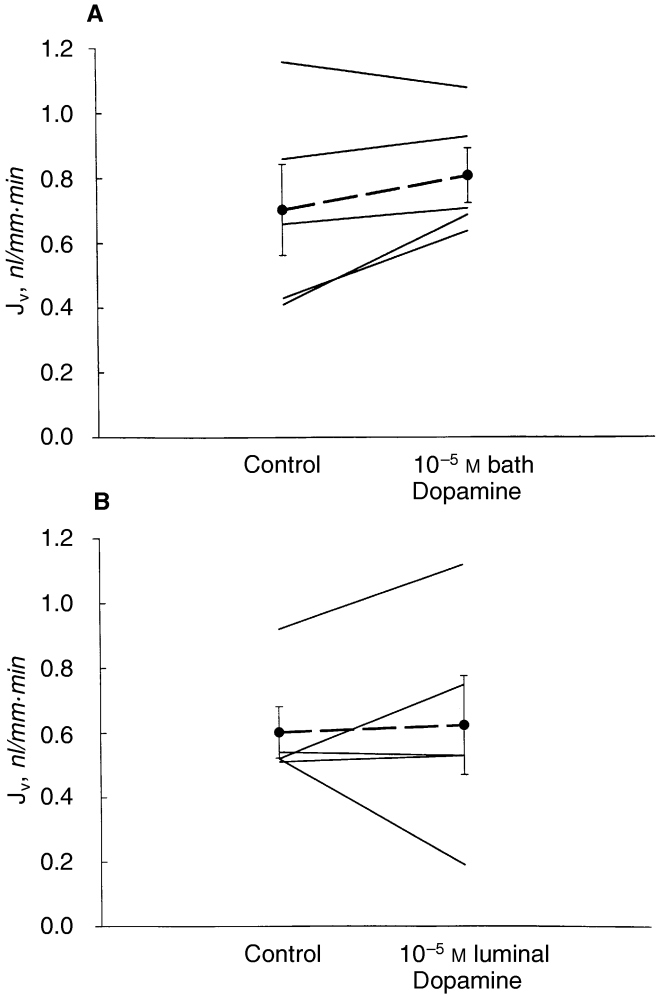

Fig. 1. Effect of 10^{-5} M bath (*A*) and luminal (*B*) dopamine on proximal convoluted tubule volume absorption (J_v).

In the next experiments we examined the effect of luminal dopamine on proximal convoluted tubule transport. Since filtered L-dopa is converted to dopamine by L-aromatic amino acid decarboxylase [13–15], and there are luminal receptors [20], dopamine may have its effect on the apical membrane. As shown in Figure 1, addition of 10^{-5} M

luminal dopamine had no effect on the rate of proximal convoluted tubule volume absorption ($N = 5$). The rate of volume absorption was 0.60 ± 0.08 nl/mm · min in the control period and 0.62 nl/mm · min after the addition of luminal dopamine. The transepithelial potential difference was −3.2 ± 0.7 mV in the control period and −3.1 ± 0.9 mV after the addition of luminal dopamine.

Effect of dopamine on proximal convoluted tubule transport in the presence of bath norepinephrine

In the next series of experiments, we examined if dopamine would modulate proximal tubule transport in the presence of 10^{-6} M bath norepinephrine. Previous studies have shown that this concentration of norepinephrine stimulates rabbit proximal convoluted tubule volume absorption and Na^+,K^+-ATPase activity [38, 39]. An effect on proximal tubule volume absorption was first measured at 10^{-7} M bath norepinephrine [38, 39], and a maximal effect was noted at 10^{-6} M bath norepinephrine [38]. As shown in Figure 2, addition of 10^{-6} M bath norepinephrine resulted in a significant increase in rate of proximal convoluted tubule transport and an increase in the lumen negative transepithelial potential difference. In the presence of bath norepinephrine, 10^{-5} M luminal dopamine inhibited proximal convoluted tubule transport and decreased the magnitude of the lumen negative transepithelial potential difference to values not different than that of the control period ($N = 5$). The rate of volume absorption was 0.65 ± 0.08 nl/mm · min in the control period and increased to 0.93 ± 0.08 nl/mm · min after addition of bath 10^{-6} M bath norepinephrine ($P < 0.01$) and decreased to 0.72 ± 0.10 nl/mm · min after addition of luminal dopamine ($P = 0.01$). To demonstrate that the exposure to bath norepinephrine did not result in a time dependent decrease in transport, we performed a time control. The rate of volume absorption was 0.67 ± 0.09 nl/mm · min in the control period and 0.95 ± 0.13 nl/mm · min after the addition of 10^{-6} M bath norepinephrine ($P < 0.05$) and was 1.05 ± 0.15 nl/mm · min with 10^{-6} M bath norepinephrine remaining in the bathing solution. The PD was −1.8 ± 0.4 mV in the control period, −2.6 ± 0.5 after addition of bath norepinephrine ($P < 0.05$) and −2.9 ± 0.5 in the time control period. Thus, the decrease in volume absorption and potential difference was due to the addition of luminal dopamine.

A dose response for the effect of luminal dopamine in the presence of 10^{-6} M bath norepinephrine is shown in Table 1. As can be seen, there was no effect on 10^{-7} M luminal dopamine. There was a tendency for 10^{-6} M luminal dopamine to inhibit proximal tubule transport in the presence of bath norepinephrine ($P = 0.06$). The decrease in potential difference was significant. This is similar to the dose response curves for bath dopamine in proximal straight tubules [28], and for the inhibition of brush border membrane vesicle Na^+/H^+ antiporter activity and proximal tubule Na^+,K^+-ATPase activity [33–37].

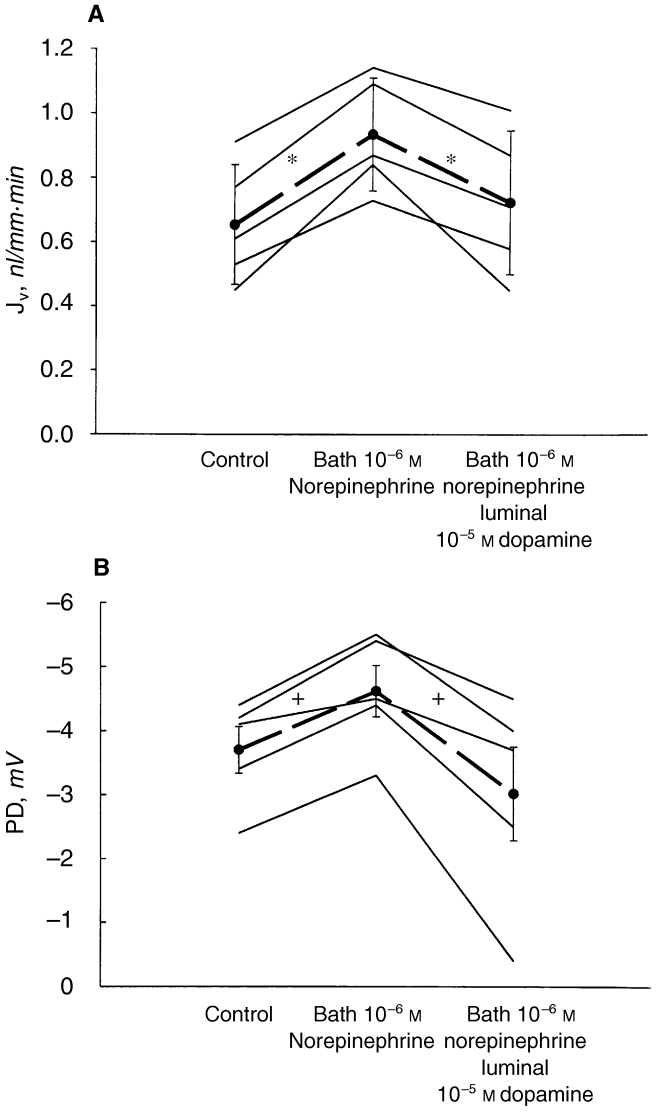

Fig. 2. Effect of 10^{-6} M bath norepinephrine and 10^{-5} M luminal dopamine in the presence of 10^{-6} M bath norepinephrine on (*A*) proximal convoluted tubule volume absorption (J_V) and (*B*) transepithelial potential difference (PD). $^*P \leq 0.01$ versus previous period; $^+P < 0.05$ versus previous period.

We next examined if bath dopamine would affect proximal convoluted tubule transport in the presence of bath norepinephrine. Five proximal convoluted tubules were perfused in the presence of 10^{-6} M bath norepinephrine. After measurements of volume absorption and transepithelial potential difference, 10^{-5} M bath dopamine was added to the bathing solution in the presence of 10^{-6} M bath norepinephrine. As shown in Figure 3, there was no effect on the rate of volume absorption or transepithelial potential difference. Volume absorption was 1.22 ± 0.18 and 1.20 ± 0.16 nl/mm · min in the control and experimental periods, respectively. Thus, luminal but not bath dopamine inhibits volume absorption in proximal convoluted tubules which have been stimulated by bath norepinephrine.

Table 1. Effect of luminal dopamine in the presence of 10^{-6} M bath norepinephrine

Experimental protocol	*N*	PD *mV*		Jv *nl/min per mm*	
		Control	Experimental	Control	Experimental
10^{-7} M Luminal dopamine	4	−2.5 ± 0.9	−2.4 ± 0.9	1.10 ± 0.32	1.06 ± 0.31
10^{-6} M Luminal dopamine	7	−3.6 ± 0.6	−2.9 ± 0.5[a]	1.28 ± 0.17	1.06 ± 0.20[b]
10^{-5} M Luminal dopamine	5	−4.6 ± 0.4	−3.0 ± 0.7[a]	0.93 ± 0.08	0.72 ± 0.10[a]

[a] $P < 0.05$
[b] $P = 0.06$

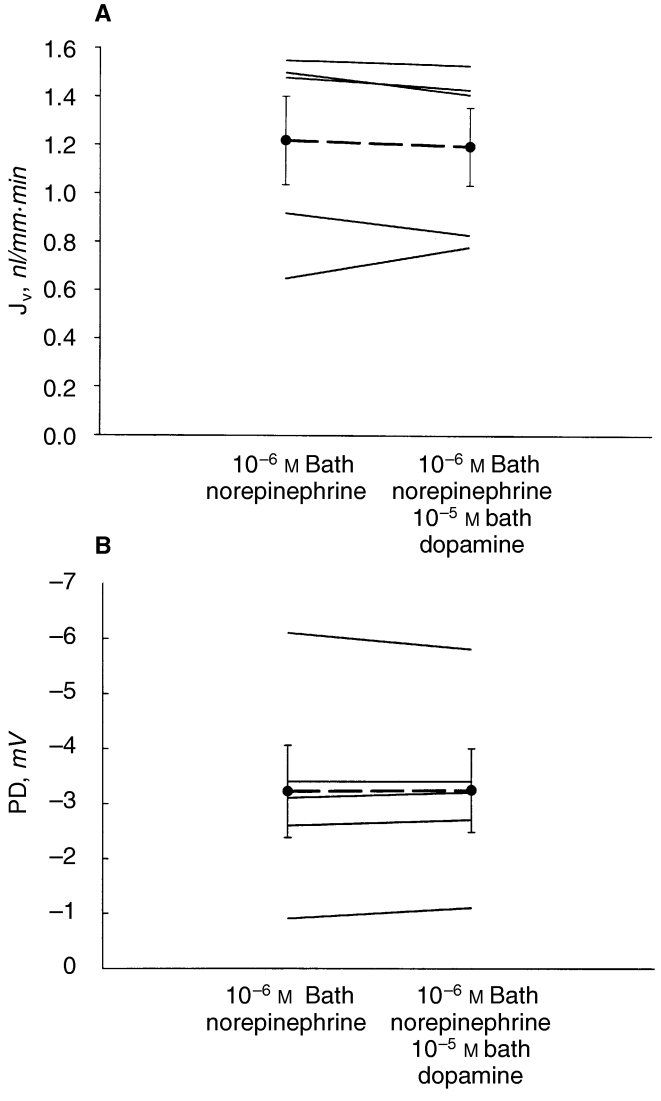

Fig. 3. Effect of 10^{-5} M bath dopamine in the presence of 10^{-6} M bath norepinephrine on volume absorption (*A*) and transepithelial potential difference (*B*).

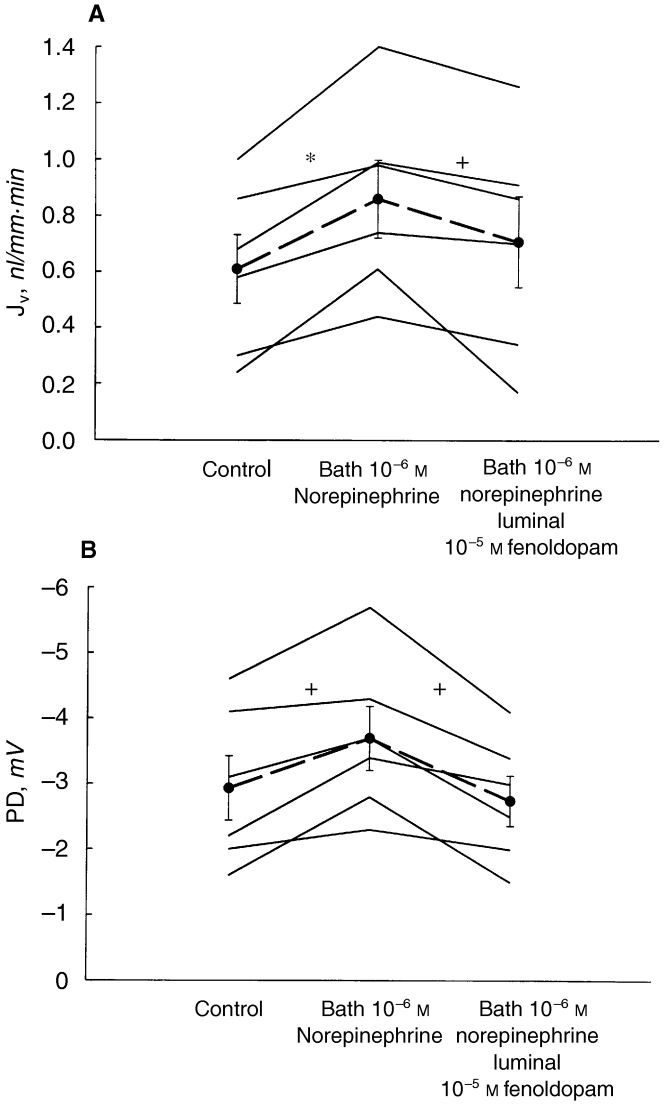

Fig. 4. Effect of 10^{-6} M bath norepinephrine and 10^{-5} M luminal fenoldopam in the presence of 10^{-6} M bath norepinephrine on proximal convoluted tubule volume absorption (*A*) and transepithelial potential difference (*B*). $^{*}P < 0.01$; $^{+}P < 0.05$.

Effect of DA_1 agonists and antagonists and a DA_2 agonist on proximal convoluted tubule transport

We next examined if the effect of luminal dopamine was mediated by DA_1 or DA_2 receptors. We first examined the effect of 10^{-5} M luminal fenoldopam, a DA_1 agonist, in the presence of bath norepinephrine. As shown in Figure 4, 10^{-6} M bath norepinephrine stimulated proximal convoluted tubule volume absorption and resulted in an increase in the lumen negative transepithelial potential difference. In the presence of bath norepinephrine, 10^{-5} M luminal fenoldopam inhibited the rate of volume absorption and

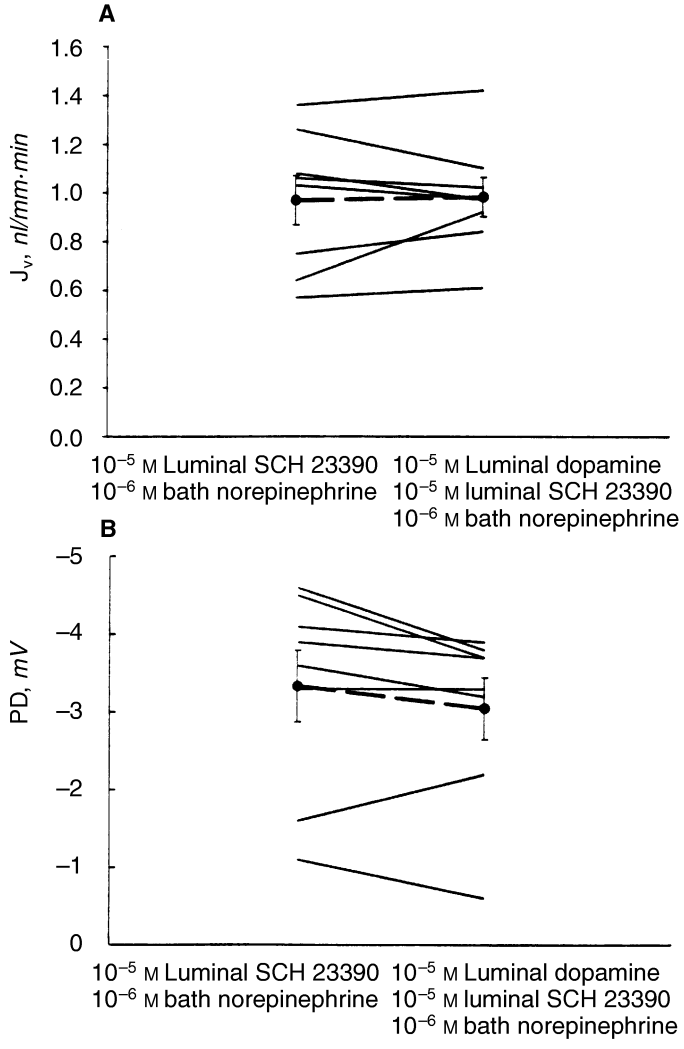

Fig. 5. Effect of 10^{-5} M luminal dopamine in the presence of 10^{-5} M luminal SCH 23390 and 10^{-6} M bath norepinephrine on volume absorption (*A*) and transepithelial potential difference (*B*).

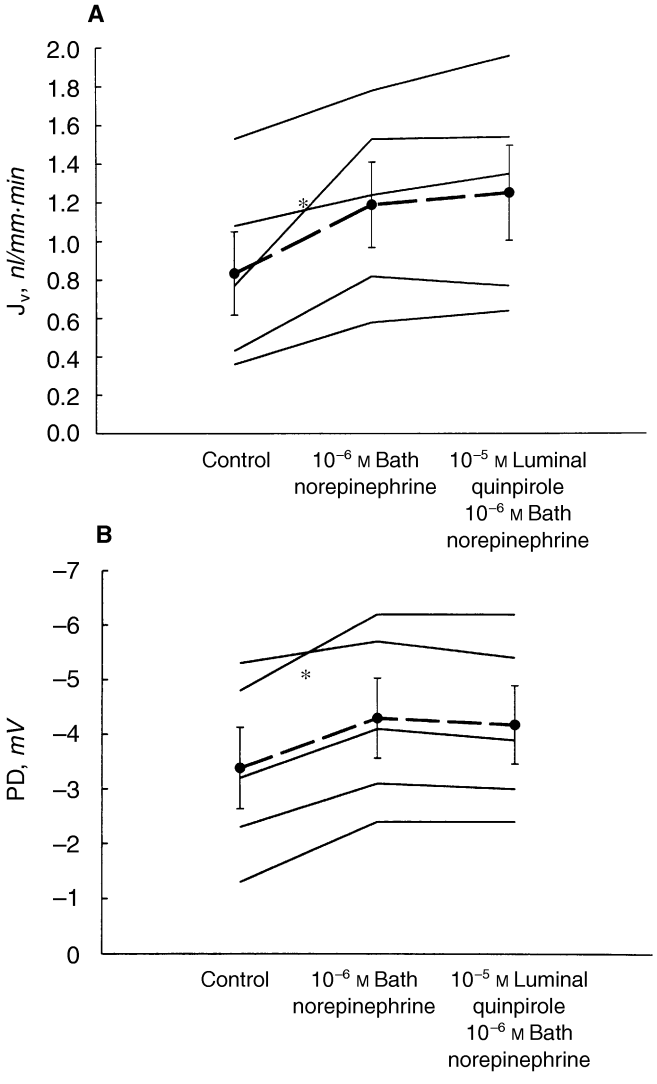

Fig. 6. Effect of 10^{-6} M bath norepinephrine and 10^{-5} M luminal quinpirole in the presence of 10^{-6} M bath norepinephrine on volume absorption (*A*) and transepithelial potential difference (*B*). *$P < 0.05$

decreased the magnitude of the transepithelial potential difference ($N = 6$). The rate of volume absorption was 0.61 ± 0.12 nl/mm · min in the control period, 0.86 ± 0.14 nl/mm · min ($P < 0.01$) after the addition of 10^{-6} M bath norepinephrine, and decreased to 0.72 ± 0.16 nl/mm · min after the addition of luminal fenoldopam ($P < 0.05$).

Whether or not the inhibition of volume absorption by luminal dopamine would be antagonized by the DA_1 antagonist, SCH 23390 was examined. Eight tubules were first perfused with an ultrafiltrate-like solution containing 10^{-5} M luminal SCH 23390 and bathed in a solution containing 10^{-6} M bath norepinephrine. In the experimental period, 10^{-5} M dopamine was added to the luminal perfusate in the presence of luminal SCH 23390 and bath norepinephrine. As shown in Figure 5, there was no effect on proximal convoluted tubule volume absorption after the addition of 10^{-5} M luminal dopamine. The rate of volume absorption was 0.97 ± 0.10 nl/mm · min in tubules with luminal SCH 23390 and bath norepinephrine and 0.98 ± 0.08 nl/mm · min upon the addition of luminal dopamine.

In the final series of experiments, we examined the effect of luminal 10^{-5} M quinpirole, a DA_2 agonist, in the presence of 10^{-6} M bath norepinephrine. As shown on Figure 6, bath norepinephrine stimulated the rate of volume absorption and increased the lumen negative transepithelial potential difference. Addition of 10^{-5} M luminal quinpirole had no effect on proximal convoluted tubule transport. The rate of proximal tubule volume absorption in the presence of 10^{-6} M bath norepinephrine was 1.19 ± 0.22 nl/mm · min and 1.25 ± 0.25 nl/mm · min upon the addition of 10^{-5} M quinpirole. Thus, the effect of luminal dopamine in the presence of bath norepinephrine is mediated via DA_1 receptors.

DISCUSSION

Several studies have demonstrated that dopamine or DA_1 agonists can produce a natriuresis independent of changes in renal hemodynamics [23, 40–42]. A direct epithelial effect of dopamine has only been demonstrated in rabbit proximal straight tubules perfused *in vitro* where dopamine and dopamine agonists inhibited volume absorption and the transepithelial potential difference [28, 30]. Similar studies where dopamine was added to the bathing solution of proximal convoluted tubules perfused *in vitro* had no effect on the rate of volume absorption [28, 30].

Renal nerves also play an important role in the regulation of salt transport by the kidney [43]. Independent of their effect on renal hemodynamics, renal nerves have a direct effect on the proximal tubule to augment sodium absorption [38, 39]. The increase in volume absorption seen in the present study with bath norepinephrine is comparable to that previously described [38, 39]. Bath norepinephrine increased the rate of proximal convoluted tubule volume absorption and the magnitude of the lumen-negative transepithelial potential difference. Both were reversed by luminal dopamine. These studies suggest that luminal dopamine may modulate proximal tubule transport under conditions when the renal nerve activity is activated or serum norepinephrine levels are elevated.

Previous studies have examined the specificity of dopamine binding in rabbit and rat kidney [21, 22]. In both rabbit and rat proximal tubules, dopamine binds specifically to DA_1 receptors, but not DA_2 receptors. The inhibition in sodium transport mediated by dopamine binding to the DA_1 receptor is via activation of both adenylate cyclase [35] and phospholipase-C [44, 45]. Our findings are consistent with these results. A nonspecific effect of 10^{-5} M dopamine is unlikely since 10^{-5} M bath and luminal dopamine had no effect on volume absorption or transepithelial potential difference in the absence of bath norepinephrine. Furthermore, in the presence of bath norepinephrine, the inhibitory effect of luminal 10^{-5} M dopamine on volume absorption was blocked by SCH 23390, a DA_1 antagonist. Addition of the DA_1 agonist fenoldopam, but not the DA_2 agonist quinpirole, to the lumen in the presence of bath norepinephrine inhibited volume absorption and the lumen negative potential difference.

Despite the fact that dopamine had not previously been shown to inhibit transport in intact proximal convoluted tubules, several studies have shown that dopamine inhibits transporters responsible for sodium reabsorption. Addition of dopamine to isolated proximal tubule segments [46] or to cortical tissue prior to the preparation of brush border membrane vesicles results in a decrease in Na^+/H^+ antiporter activity [35, 47, 48]. Dopamine inhibits Na^+/H^+ activity when added directly to brush border membrane vesicles [37, 49]. Dopamine also inhibits sodium-dependent phosphate transport in proximal straight tubules [47, 50]. Dopamine increases adenylate cyclase [35] and phospholipase-C activities [44, 45] that would be expected to result in an inhibition in proximal convuoluted tubule transport. The reason why dopamine inhibits transport in the proximal straight tubule but does not affect proximal convoluted tubule transport in the absence of peritubular norepinephrine is unclear. It is likely that dopamine antagonizes a signal transduction pathway activated by norepinephrine, however, the mechanism of this interaction is unclear at present.

Dopamine also inhibits proximal tubule transport by inhibiting Na^+,K^+-ATPase activity [8, 18, 33, 34, 36, 51, 52]. This inhibitory effect is likely mediated by dopamine synthesized from filtered L-dopa acting in an autocrine or paracrine fashion [18, 34]. In the above studies demonstrating an effect of dopamine on Na^+,K^+-ATPase activity, permeabilized tubules were employed using sodium concentrations far greater than that found within the cell. There was no effect of dopamine when physiologic concentrations of sodium were used [36]. However, dopamine did inhibit Na^+,K^+-ATPase activity in permeabilized rat proximal convoluted tubules incubated with 20 mM sodium in the presence of oxymetazoline, an alpha agonist. Furthermore, fenoldopam was found to produce a natriuresis in euvolemic rats, but not if the rats were previously denervated [36]. Interestingly, others have found that the natriuretic effect of dopamine was not significantly affected by renal nerve activity [53].

In the present study we demonstrate that 10^{-5} M luminal dopamine inhibits proximal convoluted tubule sodium transport in intact viable proximal convoluted tubules in the presence of bath norepinephrine. In this study the effect of dopamine is only observed if dopamine is added to the lumen, consistent with the autocrine/paracrine role of this hormone. These data are consistent with an effect mediated via the luminal DA_1 receptor. Our results are consistent with dopamine potentially playing a role to modulate proximal convoluted tubule transport.

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APPENDIX

Abbreviations used in this article are: DA, dopamine; J_V, volume absorption; PD, transepithelial potential difference.

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